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TO: Shailendra Kumar
Location: 5c03 / 5c18
Thursday, March 31, 2005
Art Unit: 1621
Phone: 571-272-0640
Serial Number: 09 / 923074

From: Jan Delaval
Location: Biotech-Chem Library
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jan.delaval@uspto.gov

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Scientific and Technical Information Center

SEARCH REQUEST FORM

Requester's Full Name: S. Kumar Examiner #: 69594 Date: 3/29/05

Art Unit: 1621 Phone Number: 2-0640 Serial Number: 09/923,074

Location (Bldg/Room#): RE M5C03 (Mailbox #): 5C18 Results Format Preferred (circle): PAPER DISK

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To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: Preparation of iodixanol

Inventors (please provide full names): Ole Magne Homestead

Earliest Priority Date: 2/11/1999

Search Topic:

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

For Sequence Searches Only ***Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.***

1. In a process for the preparation of iodixanol by dimerization of 5-acetamido-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-isophthalamide ("Compound A") the improvement comprising precipitating unreacted Compound A, after the dimerization, from the reaction mixture and recovering the precipitated unreacted Compound A for re-use.

2. The process of claim 1 wherein the dimerization step is carried out using epichlorohydrin; 1,3-dichloro-2-hydroxypropane; or 1,3-dibromo-2-hydroxypropane as the dimerisation agent in a solvent selected from the group consisting of non-aqueous solvents, water, and mixtures of water and one or more alcohols.

3. The process of claim 2 wherein the dimerization agent is epichlorohydrin and the solvent is 2-methoxyethanol or methanol.

4. The process of claim 1 wherein precipitation of Compound A is effected with water, optionally together with an alcoholic co-solvent.

SIN

Searcher:

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FILE LAST UPDATED: 30 Mar 2005  (20050330/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


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L66  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2005 ACS on STN
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DN   133:163953
ED   Entered STN:  20 Aug 2000
TI   Preparation of iodixanol by dimerization of 5
     -acetamido-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-
     triiodoisophthalamide (Compound A) and recycling of unreacted
     Compound A.
IN   Homestad, Ole Magne
PA   Nycomed Imaging AS, Norway; Skailes, Humphrey John
SO   PCT Int. Appl., 13 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
IC   ICM  C07C231-24
     ICS  C07C237-46
CC   25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
FAN.CNT 1
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             IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
             MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,
             SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM,
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PRAI	GB 1999-3109	A	19990211	<--		
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CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2000047549	ICM	C07C231-24
	ICS	C07C237-46
US 2002010368	ECLA	C07C231/08 <--

OS CASREACT 133:163953

AB A process for the preparation of **iodixanol** by **dimerization** of **5-acetamido**-N,N'-bis(2,3-**dihydroxypropyl**)-2,4,6-**triiodoisophthalamide** (Compound A) in which, after the **dimerization** step, unreacted Compound A is precipitated from the reaction mixture and recovered for re-use. The process substantially increases the net yield of **iodixanol** and simplifies its purification Thus, Compound A and NaOH in 2-**methoxyethanol** at 15° was treated with concentrate HCl and then with **epichlorohydrin** to give after 46 h a solution containing 49.6% **iodixanol.** The mixture was treated with HCl to pH 10.8, seeded with Compound A, further acidified to pH 4, and filtered to give a filtrate comprising 94.3% Compound A and 5.1% **iodixanol.** Purified recovered Compound A was combined with fresh Compound A for use in a new **dimerization** which gave nearly identical results.

ST **iodixanol** prepn; **acetamidobisdihydroxypropyltriiodoisophtha lamide dimerization** recycling

IT **92339-11-2P, Iodixanol**
RL: **IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)**
(preparation of **iodixanol** by **dimerization** of **5-acetamido**-N,N'-bis(2,3-**dihydroxypropyl**)-2,4,6-**triiodoisophthalamide** (Compound A) and recycling of unreacted Compound A)

IT **96-21-9, 1,3-Dibromo-2-hydroxypropane 96-23-1, 1,3-Dichloro-2-hydroxypropane 106-89-8, Epichlorohydrin**, reactions **31127-80-7**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of **iodixanol** by **dimerization** of **5-acetamido**-N,N'-bis(2,3-**dihydroxypropyl**)-2,4,6-**triiodoisophthalamide** (Compound A) and recycling of unreacted Compound A)

RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

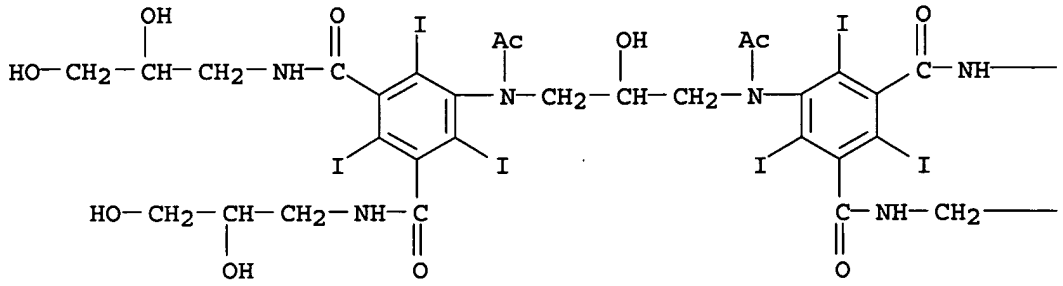
(1) Nyegaard & Co As; EP 0108638 A 1984 HCAPLUS

IT **92339-11-2P, Iodixanol**
RL: **IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)**
(preparation of **iodixanol** by **dimerization** of **5-acetamido**-N,N'-bis(2,3-**dihydroxypropyl**)-2,4,6-**triiodoisophthalamide** (Compound A) and recycling of unreacted Compound A)

RN 92339-11-2 HCAPLUS

CN 1,3-Benzenedicarboxamide, 5,5'-[(2-hydroxy-1,3-propanediyl)bis(acetylimino)]bis[N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo- (9CI) (CA INDEX NAME)

PAGE 1-A



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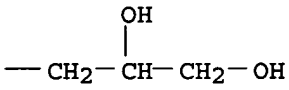

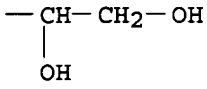

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RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of **iodixanol** by **dimerization** of 5 -**acetamido**-N,N'-bis(2,3-**dihydroxypropyl**)-2,4,6-**triiodoisophthalamide** (Compound A) and recycling of unreacted Compound A)

RN 96-21-9 HCAPLUS
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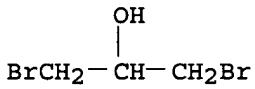

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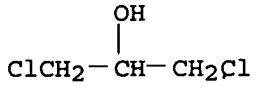
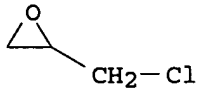
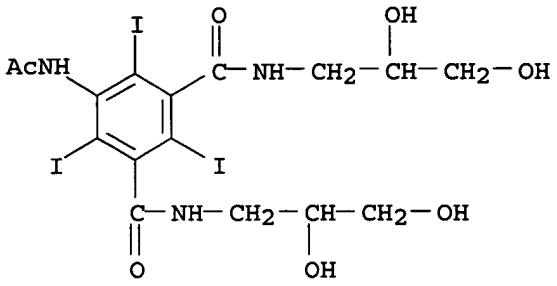


RN 106-89-8 HCAPLUS
CN Oxirane, (chloromethyl)- (9CI) (CA INDEX NAME)



RN 31127-80-7 HCAPLUS
CN 1,3-Benzenedicarboxamide, 5-(acetylamino)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo- (9CI) (CA INDEX NAME)



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AN **1984:551599** HCAPLUS
DN **101:151599**
ED Entered STN: 27 Oct 1984
TI X-ray contrast agents
IN Hansen, Per Egil; Holtermann, Hugo; Wille, Knut
PA Nyegaard og Co. A/S, Norway
SO Eur. Pat. Appl., 20 pp.
CODEN: EPXXDW
DT Patent
LA English
IC C07C103-78; A61K049-04
CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 1, 63
FAN.CNT 1

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PI	EP 108638	A1	19840516	EP 1983-306766	19831107
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	DK 160868	B	19910429		
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	AT 20733	E	19860815	AT 1983-306766	19831107
	US 5349085	A	19940920	US 1992-960231	19921013
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	US 1986-924925	B1	19861030		
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CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
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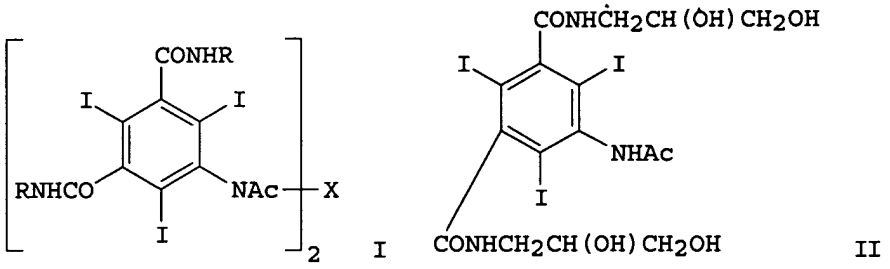


I II

AB Bis(triiodophenyl)hydroxyalkanes I [R = CH(CH2OH)2, CH2CH(OH)CH2OH; X = CH2CH(OH)CH2, CH2CH(OH)CH(OH)CH2] were prepared Thus, acetylaminoisophthalamide II reacted with ClCH2CH(OH)CH(OH)CH2Cl to give I [R = CH2CH(OH)CH2OH, X = CH2CH(OH)CH(OH)CH2] (III). III had a viscosity of 8.7 cP at 37° and 300 mg iodine/mL and had a urinary excretion level of 230 mg iodine/mL in rabbits when administered at 200 mg iodine/kg.

ST bisiodophenylhydroxyalkane prepn radiog; x ray contrast agent bisiodophenylhydroxyalkane; iodophenylhydroxyalkane prepn radiog

IT Radiography
(contrast agents for, bis(iodophenyl)hydroxyalkanes)

IT 60166-98-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(acylation of)

IT **106-89-8**, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(alkylation by, of (acetylamino)(triiodo)isophthalamide)

IT **31127-80-7**
RL: RCT (Reactant); RACT (Reactant or reagent)
(alkylation of)

IT 2419-73-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and alkylation by, of acetylamino(triiodo)isophthalamide)

IT 87932-07-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and alkylation of, with **epichlorohydrin**)

IT 92339-10-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrolysis of)

IT 92339-12-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and urinary excretion of)

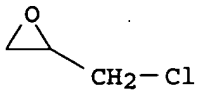
IT 92339-08-7P 92339-09-8P **92339-11-2P**
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(preparation, viscosity, and urinary excretion of)

IT 1464-53-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with isophthalamide or hydrogen chloride)

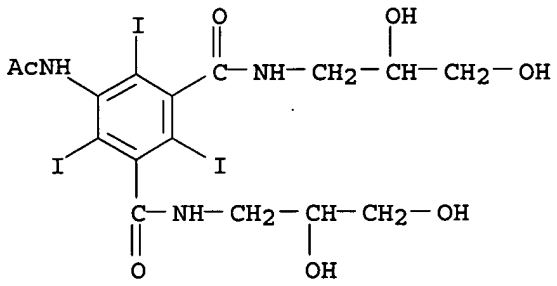
IT **106-89-8**, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(alkylation by, of (acetylamino)(triiodo)isophthalamide)

RN 106-89-8 HCAPLUS

CN Oxirane, (chloromethyl)- (9CI) (CA INDEX NAME)



IT **31127-80-7**
RL: RCT (Reactant); RACT (Reactant or reagent)
(alkylation of)
RN 31127-80-7 HCAPLUS
CN 1,3-Benzenedicarboxamide, 5-(acetylamino)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo- (9CI) (CA INDEX NAME)



IT **92339-11-2P**
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(preparation, viscosity, and urinary excretion of)
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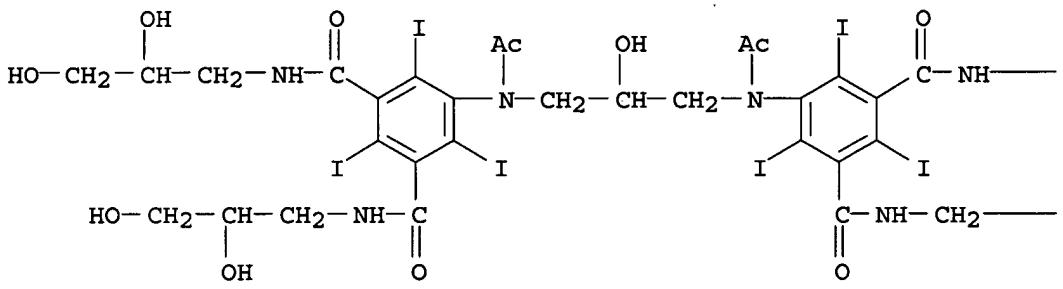
CN 1,3-Benzenedicarboxamide, 5,5'-[(2-hydroxy-1,3-propanediyl)bis(acetylimino)]bis[N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo- (9CI) (CA INDEX NAME)

PAGE 1-A



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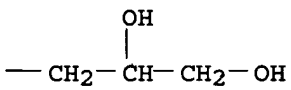

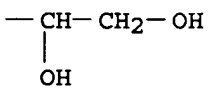

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AN   2000-524525 [47]   WPIX
DNC  C2000-155833
TI   Preparation of iodixanol useful as an x-ray contrast agent, by
     dimerization process with crystallization and recycling of starting
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DC   B05
IN   HOMESTAD, O M
PA   (NYCO-N) NYCOMED IMAGING AS; (AMER-N) AMERSHAM HEALTH AS; (SKAI-I) SKAILES
     H J; (HOME-I) HOMESTAD O M
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     US 2002010368   A1 20020124 (200210)             C07C233-64
     KR 2001102005   A  20011115 (200231)             C07C231-24
     HU 2001005096   A2 20020429 (200238)             C07C231-24
     CN 1340042      A  20020313 (200245)             C07C231-24
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ES 2206190 T3 20040516 (200434) C07C231-24

ADT WO 2000047549 A1 WO 2000-GB413 20000210; AU 2000024495 A AU 2000-24495 20000210; NO 2001003881 A WO 2000-GB413 20000210, NO 2001-3881 20010809; EP 1150943 A1 EP 2000-902754 20000210, WO 2000-GB413 20000210; CZ 2001002891 A3 WO 2000-GB413 20000210, CZ 2001-2891 20000210; US 2002010368 A1 Provisional US 1999-121539P 19990225, Cont of WO 2000-GB413 20000210, US 2001-923074 20010806; KR 2001102005 A KR 2001-710055 20010809; HU 2001005096 A2 WO 2000-GB413 20000210, HU 2001-5096 20000210; CN 1340042 A CN 2000-803705 20000210; JP 2002536429 W JP 2000-598470 20000210, WO 2000-GB413 20000210; EP 1150943 B1 EP 2000-902754 20000210, WO 2000-GB413 20000210; DE 60005143 E DE 2000-00005143 20000210, EP 2000-902754 20000210, WO 2000-GB413 20000210; ES 2206190 T3 EP 2000-902754 20000210

FDT AU 2000024495 A Based on WO 2000047549; EP 1150943 A1 Based on WO 2000047549; CZ 2001002891 A3 Based on WO 2000047549; HU 2001005096 A2 Based on WO 2000047549; JP 2002536429 W Based on WO 2000047549; EP 1150943 B1 Based on WO 2000047549; DE 60005143 E Based on EP 1150943, Based on WO 2000047549; ES 2206190 T3 Based on EP 1150943

PRAI GB 1999-3109 19990211

IC ICM C07C000-00; C07C231-08; C07C231-24; C07C233-64
ICS C07C237-46

AB WO 200047549 A UPAB: 20000925
NOVELTY - A new process for the preparation of **iodixanol** comprises dimerization of 5-acetamido-N,N'-bis(2,3-dehydroxypropyl)-2,4,6-triiodo-isophthalamide with recycling of unreacted material.

DETAILED DESCRIPTION - A novel process for the preparation of **iodixanol** comprises dimerization of 5-acetamido-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-isophthalamide (Compound (A)) in which, after the dimerization step, unreacted (A) is precipitated from the reaction mixture and recovered for re-use.

USE - The **iodixanol** (1,3-bis(acetamido)-N,N'-bis(3,5-bis(2,3-dihydroxypropylaminocarbonyl)-2,4,6-triiodophenyl)-2-hydroxypropane) is used as a non-ionic X-ray contrast agent.

ADVANTAGE - The unreacted (A) from one dimerization batch can be recovered from the reaction mixture by a simple process and reused in a latex batch which increases the net yield from successive batches on an industrial scale dramatically. Additionally, the removal of most of the unreacted Compound (A) from the reaction mixture allows the expensive preparative liquid chromatography purification to be replaced by conventional crystallization methods, still providing **iodixanol** suitable for pharmaceutical use.

Dwg.0/0

FS CPI

FA AB; DCN

MC CPI: B10-B01; B12-K07

TECH UPTX: 20000925
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Process: Preferably the dimerization step is carried out using **epichlorohydrin**, 1,3-dichloro-2-hydroxypropane or 1,3-dibromo-2-hydroxypropane as the dimerization agent in a non-aqueous solvent or in water or a mixture of water and one or more alcohols, e.g. the dimerization agent is **epichlorohydrin** and the solvent is 2-methoxyethanol or methanol. The precipitation of (A) is effected with water, optionally together with an alcoholic co-solvent. The mixture may be adjusted to pH 10-11 with acid to provoke precipitation, the temperature adjusted if necessary to 15-40 degrees C and the solution optionally seeded with crystals of (A). The method may further comprise adding acid to a pH of 2-5. The recovered compound (A) may be re-used in a subsequent process for the preparation of **iodixanol**. After separation of compound (A), the **iodixanol** -containing mixture is preferably purified without the use of chromatographic methods.

ABEX UPTX: 20000925
EXAMPLE - 5-Acetamido-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-

isophthalamide (A) (366 g) was dissolved in a solution of NaOH (23 g) in 2-methoxyethanol (360 ml) at 50 degrees C. The temperature was decreased to 15 degrees C when all solids were dissolved, and concentrated HCl (28 g) was added to the solution. **Epichlorohydrin** (13 g) was added in one portion, and the reaction was monitored by HPLC. After 46 hours the content of **iodixanol** in the reaction mixture was 49.6 %. Water (575 ml) was added, and the temperature was increased to 19 degrees C. The solution was at this time clear, so no further addition of NaOH was necessary. The pH of the resulting suspension was further pH-adjusted with 18 % HCl to pH 4.0. The suspension was left with stirring overnight before filtration and washing with water (60 ml) on the filter. The filtrate was further desalinated and crystallized by conventional methods, providing **iodixanol** suitable for pharmaceutical use. The material on the filter was analyzed on HPLC, showing 94.3 % Compound (A) and 5.1 % **iodixanol.** The recovered Compound (A) from was taken directly from the filter without drying and completely dissolved in water (440 ml) and 50 % aqueous NaOH (15 ml). The solution was filtered through a 3 microm filter to remove traces of insoluble matter, and some more water (50 ml) was added to the filtrate. methanol (95 ml) was added to the solution, and the temperature was increased to 60 degrees C. The pH was reduced from 11.5 to 9.8 with 18 % HCl, and 0.8 g seeds of Compound (A) was added. After 30 minutes, the pH was further reduced to 6 with 18 % HCl. The temperature was gradually reduced to 15 degrees C, and the precipitated material was filtered, washed with methanol (140 ml) and dried under vacuum at 60 degrees C. The yield of pure Compound (A) (at least 99 % by HPLC) was 118 g, corresponding to 32 % of the starting material in (A).

L78 ANSWER 2 OF 2 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 1998-179356 [16] WPIX
DNC C1998-057657
TI N-Alkyl-acylamino-phenyl carboxylic acids (derivatives) preparation - by liquid phase acylation and subsequent N-alkylation of aminophenyl-carboxylic acids or derivatives.
DC B05
IN HOLMAAS, L T; INGVOLDSTAD, O E; GULBRANDSEN, T; GILBRANDSENSEN, T
PA (NYCO-N) NYCOMED IMAGING AS; (COCK-I) COCKBAIN J R M; (AMER-N) AMERSHAM HEALTH AS
CYC 79
PI WO 9808805 A1 19980305 (199816)* EN 17 C07C231-08
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9740267 A 19980319 (199831) C07C231-08
US 5840967 A 19981124 (199903) C07C229-00
NO 9900890 A 19990225 (199923) C07C233-07
EP 923537 A1 19990623 (199929) EN C07C231-08
R: AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV MC NL PT RO SE SI
CZ 9900670 A3 19990811 (199937) C07C231-08
BR 9711358 A 19990817 (199954) C07C231-08
CN 1228762 A 19990915 (200001) C07C231-08
HU 9903852 A2 20000328 (200025) C07C231-08
AU 717842 B 20000406 (200027) C07C231-08
SK 9900263 A3 20000313 (200032) C07C231-08
NZ 334818 A 20000825 (200049) C07C231-08
MX 9901933 A1 19991001 (200103) C07C231-08
JP 2000517313 W 20001226 (200104) 18 C07C231-08
KR 2000035944 A 20000626 (200111) C07C231-08
EP 923537 B1 20011031 (200169) EN C07C231-08
R: AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV MC NL PT RO SE

SI
DE 69707901 E 20011206 (200203) C07C231-08
ES 2167014 T3 20020501 (200236) C07C231-08
US 6610885 B1 20030826 (200357) C07C233-05

ADT WO 9808805 A1 WO 1997-GB2335 19970829; AU 9740267 A AU 1997-40267 19970829; US 5840967 A Provisional US 1996-29143P 19961021, US 1997-845134 19970421; NO 9900890 A WO 1997-GB2335 19970829, NO 1999-890 19990225; EP 923537 A1 EP 1997-937743 19970829, WO 1997-GB2335 19970829; CZ 9900670 A3 WO 1997-GB2335 19970829, CZ 1999-670 19970829; BR 9711358 A BR 1997-11358 19970829, WO 1997-GB2335 19970829; CN 1228762 A CN 1997-197523 19970829; HU 9903852 A2 WO 1997-GB2335 19970829, HU 1999-3852 19970829; AU 717842 B AU 1997-40267 19970829; SK 9900263 A3 WO 1997-GB2335 19970829, SK 1999-263 19970829; NZ 334818 A NZ 1997-334818 19970829, WO 1997-GB2335 19970829; MX 9901933 A1 MX 1999-1933 19990226; JP 2000517313 W WO 1997-GB2335 19970829, JP 1998-511401 19970829; KR 2000035944 A WO 1997-GB2335 19970829, KR 1999-701685 19990227; EP 923537 B1 EP 1997-937743 19970829, WO 1997-GB2335 19970829; DE 69707901 E DE 1997-607901 19970829, EP 1997-937743 19970829, WO 1997-GB2335 19970829; ES 2167014 T3 EP 1997-937743 19970829; US 6610885 B1 Provisional US 1996-29143P 19961021, Cont of US 1997-845134 19970421, US 1998-98350 19980617

FDT AU 9740267 A Based on WO 9808805; EP 923537 A1 Based on WO 9808805; CZ 9900670 A3 Based on WO 9808805; BR 9711358 A Based on WO 9808805; HU 9903852 A2 Based on WO 9808805; AU 717842 B Previous Publ. AU 9740267, Based on WO 9808805; NZ 334818 A Based on WO 9808805; JP 2000517313 W Based on WO 9808805; KR 2000035944 A Based on WO 9808805; EP 923537 B1 Based on WO 9808805; DE 69707901 E Based on EP 923537, Based on WO 9808805; ES 2167014 T3 Based on EP 923537; US 6610885 B1 Cont of US 5840967

PRAI GB 1996-18055 19960829

IC ICM C07C229-00; C07C231-08; C07C233-05; C07C233-07
ICS A61K049-04; C07C233-00; C07C233-53; C07C237-46

AB WO 9808805 A UPAB: 19980421
Preparation of an N-alkyl-acylamino-phenyl-carboxylic acid (I) or derivative by liquid phase acylation and subsequent N-alkylation of a corresponding aminophenyl-carboxylic acid (II) or derivative is improved by the addition of an alkylating agent to a solution containing the reaction products, to effect the N-alkylation.

Also claimed is the preparation of (I) by acylating (II) in a liquid phase, base hydrolysing the acylated product to remove O-acyl groups from the N-acylamino intermediate and then N-alkylating the intermediate while maintaining the liquid phase at a basic pH.

(II) has a total of three amino and carboxyl groups on the phenyl ring. (II) is especially an alkylamino-carbonyl- triiodo-phenyl compound or 2,4,6-triiodo-2,5-bis(alkylamino carbonyl)aniline, e.g. 5-amino-N,N'-bis-(2,3-dihydroxypropyl)- 2,4,6-triiodophthalamide. (II) also preferably contains an aminoalkylcarbonyl group carrying one or more hydroxyl groups and containing up to 6C.

The alkylating agent is preferably 1-halo-2,3-propane diol, glycidol, 1-halo-3-methoxy-2-propanol, 1,3-dihalo-2-propanol or **epichlorohydrin.** The acylating agent is preferably an acid halide or acetic anhydride.

USE - The process is used for the preparation of the contrast agents iomeprol, ioversol, ioxilan, iotrolan, ioxaglate, iodecimol, 2-iopyrol, 2-iopiperidol, iohexol, iopentol and **iodixanol.**

ADVANTAGE - Work-up of the intermediate before N-alkylation may be avoided without loss of yield or purity of the final product and without undue complication of the purification procedure for that product.

Dwg.0/0

FS CPI

FA AB; DCN

MC CPI: B10-D03; B12-K07

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=> d his

     (FILE 'HOME' ENTERED AT 13:37:37 ON 31 MAR 2005)
               SET COST OFF

     FILE 'REGISTRY' ENTERED AT 13:37:47 ON 31 MAR 2005
               E IODIXANOL/CN
L1             1 S E3
L2             0 S 92339-11-2/CRN
               E EPICHLOROHYDRIN/CN
L3             1 S E3
L4             1 S E6
L5             1 S E10,E12
               E 1,3-DICHLORO-2-HYDROXYPROPANE/CN
L6             1 S E3
L7            93 S 96-23-1/CRN
               E 1,3-DIBROMO-2-HYDROXYPROPANE/CN
L8             1 S E3
L9            26 S 96-21-9/CRN
               E 1,3-DIFLUORO-2-HYDROXYPROPANE/CN
               E 1,3-DIIODO-2-HYDROXYPROPANE/CN
               E 2-METHOXYETHANOL/CN
L10            1 S E3
               E METHANOL/CN
L11            1 S E3

     FILE 'HCAPLUS' ENTERED AT 13:45:31 ON 31 MAR 2005
L12            1 S US20020010368/PN OR (US2001-923074# OR WO2000-GB413 OR GB99-3
L13            4 S 5 ACETAMIDO (L) DIHYDROXYPROPYL (L) TRIIODOISOPHTHALAMIDE
L14           17 S ?ACETAMIDO?(L)?HYDROXYPROPYL?(L)?ISOPHTHALAMIDE?

     FILE 'REGISTRY' ENTERED AT 14:13:07 ON 31 MAR 2005
L15            1 S 111453-49-7
L16            1 S 66108-95-0

     FILE 'HCAPLUS' ENTERED AT 14:14:03 ON 31 MAR 2005
L17          569 S IOHEXOL
L18            4 S L17 AND L13,L14

     FILE 'REGISTRY' ENTERED AT 14:15:01 ON 31 MAR 2005

     FILE 'HCAPLUS' ENTERED AT 14:16:35 ON 31 MAR 2005
L19          644 S L16
L20          416 S LOHEXOL OR ACCUDENZ OR EXYPAQUE OR NYCODENZ OR OMNIPAQUE

     FILE 'REGISTRY' ENTERED AT 14:16:47 ON 31 MAR 2005
L21            1 S 66108-95-0/CRN

     FILE 'HCAPLUS' ENTERED AT 14:16:52 ON 31 MAR 2005
L22          926 S L13,L14,L17,L19,L20
L23          211 S L1
L24          252 S IODIXANOL OR VISIPAQUE
L25          259 S L23,L24
L26          105 S L25 AND L22
L27            4 S L26 AND L3-L5
L28            4 S L26 AND EPICHLOROHYDRIN?
L29            0 S L26 AND EPI CHLOROHYDRIN?
L30            2 S L26 AND L6,L8
L31            1 S L26 AND 1 3 ()(DICHLORO OR DIBROMO)()2 HYDROXYPROPANE
L32            0 S L26 AND L7,L9
L33            0 S L26 AND L10
L34            1 S L26 AND (METHOXYETHANOL OR METHOXY ETHANOL)
L35            3 S L26 AND (L11 OR MEOH OR METHANOL OR METHYLALCOHOL OR METHYL A
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L36           8 S L27,L28,L30,L31,L34,L35
L37          20 S L25 (L) PREP+NT/RL
L38           5 S L36 AND L37
L39           1 S L26 AND 1 3 ()(DICHLORO OR DIBROMO)()2 PROPANOL
L40           5 S L38,L39
L41           1 S L12 AND L40
                E HOMESTAD O/AU
L42           4 S E4
                E NYCOMED/PA,CS
L43         582 S NYCOMED?/PA,CS
L44          41 S L42,L43 AND L25
L45          23 S L44 AND L26
L46           5 S L45 AND L36,L38-L41
L47          24 S L26 AND ?DIMER?
L48           1 S L47 AND L27-L41
L49           0 S L47 AND DIMERIS?
L50           1 S L47 AND DIMERIZ?
L51           1 S L48,L50
L52          23 S L47 NOT L51
L53          15 S L1(L)PREP+NT/RL
L54           8 S L53 AND L22
L55           1 S L54 AND L47
L56           1 S L51,L55 AND L12-L14,L17-L20,L22-L55

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L58           0 S 31127-80-7/CRN

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L59           7 S L57 AND L25
L60           4 S L59 AND L3-L11
L61           4 S L59 AND (EPICHLOROHYDRIN? OR METHOXYETHANOL OR METHANOL OR ME
L62           4 S L60,L61
L63           1 S L62 AND ?DIMER?
L64           3 S L62 NOT L63
                SEL RN 3
                SEL DN AN 3
L65           1 S E12-E14 AND L64
L66           2 S L63,L65 AND L12-L14,L17-L20,L22-L56,L59-L65
L67           3 S L59 NOT L62

     FILE 'HCAPLUS' ENTERED AT 14:35:32 ON 31 MAR 2005

     FILE 'CASREACT' ENTERED AT 14:36:38 ON 31 MAR 2005
L68           1 S L1/PRO
L69           1 S L1

     FILE 'WPIX' ENTERED AT 14:37:29 ON 31 MAR 2005
L70          48 S L24/BIX
                E IODIXANOL/DCN
                E E3+ALL
L71          65 S E2 OR L70
                E EPICHLOROHYDRIN/DCN
                E E2+ALL
L72        1690 S E2 OR 0798/DRN
                E 1,3-DICHLORO-2-HYDROXYPROPANE/DCN
                E 1,3-DIBROMO-2-HYDROXYPROPANE/DCN
                E 2-HYDROXYPROPANE/DCN
                E 1,3-DIBROMO-2-HYDROXYPROPANE/CN
L73        9416 S (EPICHLOROHYDRIN? OR EPI CHLOROHYDRIN?)/BIX
L74           2 S L71 AND L72,L73
                E R10478+ALL/DCN
L75          12 S E1
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                E R03250+ALL/DCN
L76           34 S E1
L77            1 S L71 AND L75,L76
L78            2 S L74,L77

     FILE 'WPIX' ENTERED AT 14:41:20 ON 31 MAR 2005

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